

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference X15463	FOR FURTHER ACTION See Notification of Transmittal of International Preliminary Examination Report (Form PCT/PEA/416)	
International application No. PCT/US 03/39119	International filing date (<i>day/month/year</i>) 31.12.2003	Priority date (<i>day/month/year</i>) 06.01.2003
International Patent Classification (IPC) or both national classification and IPC C07D231/12		
Applicant ELI LILLY AND COMPANY et al		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 5 sheets, including this cover sheet.

☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

These annexes consist of a total of 4 sheets.

3. This report contains indications relating to the following items:

- I ☒ Basis of the opinion
- II ☐ Priority
- III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- IV ☐ Lack of unity of invention
- V ☒ Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- VI ☐ Certain documents cited
- VII ☐ Certain defects in the international application
- VIII ☐ Certain observations on the international application

Date of submission of the demand 10.08.2004	Date of completion of this report 25.02.2005
Name and mailing address of the international preliminary examining authority: <div style="display: flex; align-items: center;"> <div> European Patent Office - P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk - Pays Bas Tel. +31 70 340 - 2040 Tx: 31 651 epo nl Fax: +31 70 340 - 3016 </div> </div>	Authorized Officer De Jong, B Telephone No. +31 70 340-2833



**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT**

International application No. **PCT/US 03/39119**

I. Basis of the report

1. With regard to the **elements** of the international application (*Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17)*):

Description, Pages

1-181 as originally filed

Claims, Pages

182, 184, 185, 187-189, as originally filed
191-193, 195-208

183, 186, 190, 194 received on 04.01.2005 with letter of 04.01.2005

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
☐ the language of publication of the international application (under Rule 48.3(b)).
☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.
☐ filed together with the international application in computer readable form.
☐ furnished subsequently to this Authority in written form.
☐ furnished subsequently to this Authority in computer readable form.
☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
☐ the claims, Nos.:
☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)).

(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

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EXAMINATION REPORT**

International application No. **PCT/US 03/39119**

6. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 1-48,52-67

because:

☒ the said international application, or the said claims Nos. 55-59,61,63,64 (with respect to industrial application) relate to the following subject matter which does not require an international preliminary examination (specify):

see separate sheet

☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☒ no international search report has been established for the said claims Nos. 1-48,52-67 (all in part)

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

☐ the written form has not been furnished or does not comply with the Standard.

☐ the computer readable form has not been furnished or does not comply with the Standard.

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes: Claims	1-67
	No: Claims	
Inventive step (IS)	Yes: Claims	
	No: Claims	1-67
Industrial applicability (IA)	Yes: Claims	1-54,60,62,65-67
	No: Claims	

2. Citations and explanations

see separate sheet

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

Claims 55-59,61,63,64 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(I) PCT).

A complete international preliminary examination of the present application is limited to those parts of the claims for which a complete international search report was established (Rule 66.1(e) PCT), i.e. to the compounds according to claims 49-51 and there pharmaceutical use. **It should in particular be understood that any positive statement as to novelty and/or inventive step exclusively relates to said limited subject-matter.**

Re Item V

Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

Reference is made to the following documents:

- D1: JP 11 130753 A (TAIHO YAKUHHIN KOGYO KK) 18 May 1999
- D2: WO 01/16120 A (DOMINIANNI SAMUEL J ;8 March 2001
- D3: WO 02/100403 A (GONZALEZ-GARCIA 19 December 2002
- D4: EP-A-0 442 448 (SQUIBB BRISTOL MYERS CO) 21 August 1991

The subject-matter claimed in the present application is novel insofar it relates to the compounds according to claim 49-51 and their use.

2) The present application does not meet the criteria of Article 33(1) PCT, because the subject-matter of claims 1-67 (insofar it is novel) does not involve an inventive step in the sense of Article 33(3) PCT:

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT - SEPARATE SHEET**

International application No. PCT/US 03/39119

The present application relates to PPAR inhibitors according to claim 1 which can be used against e.g. diabetes and lipid disorders. The problem underlying the present application is to provide alternative PPAR inhibitors.

Documents D2 and D3 disclose structurally related PPAR inhibitors and document D1 discloses pharmaceutical compounds which can be used against the same and/or similar diseases as the compounds of the present application. In view of these documents it was obvious for the skilled person to come to certain compounds claimed in the present application.

It is furthermore noted that the activity of the compounds according to the present application is not substantiated sufficiently. The only quantitative statement concerning the compounds is given on page 167, lines 3-6. This statement indicates that only part of the compounds of the examples (which are especially useful for modulating a PPAR receptor) solve the problem.

3) For the assessment of the present claims 55-59,61,63,64 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States.

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R19, R20, R21, R22, R23, R24 and R25 are each independently selected from the group consisting of hydrogen, C₁-C₆ alkyl and aryl;

(c) R2 is selected from the group consisting of C₀-C₈ alkyl and C₁-4-heteroalkyl;

(d) X is selected from the group consisting of a single bond, O, S, S(O)₂ and N;

(e) U is an aliphatic linker wherein one carbon atom of the aliphatic linker is optionally replaced with O, NH or S, and wherein such aliphatic linker is optionally substituted with from one to four substituents each independently selected from R30;

(f) Y is selected from the group consisting of C, NH, and a single bond;

(g) E is C(R3)(R4)A and wherein

(i) A is selected from the group consisting of carboxyl, tetrazole, C₁-C₆ alkyl nitrile, carboxamide, sulfonamide and acylsulfonamide; wherein sulfonamide, acylsulfonamide and tetrazole are each optionally substituted with from one to two groups independently selected from R⁷;

(ii) each R⁷ is independently selected from the group consisting of hydrogen, C₁-C₆ haloalkyl, aryl C₀-C₄ alkyl and C₁-C₆ alkyl;

(iii) R3 is selected from the group consisting of hydrogen, C₁-C₅ alkyl, and C₁-C₅ alkoxy; and

(iv) R4 is selected from the group consisting of H, C₁-C₅ alkyl, C₁-C₅ alkoxy, aryloxy, C₃-C₆ cycloalkyl, and aryl C₀-C₄ alkyl, and R3 and R4 are optionally combined to form a C₃-C₄

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- alkyl, aryl-C₁₋₄-heteroalkyl, heteroaryl-C₀₋₄-alkyl, and C₃₋₆ cycloalkylaryl-C₀₋₂-alkyl, and, wherein C₁₋₈ alkyl, C₁₋₈ alkenyl, aryl-C₀₋₄-alkyl, aryl-C₁₋₄-heteroalkyl, heteroaryl-C₀₋₄-alkyl, C₃₋₆ cycloalkylaryl-C₀₋₂-alkyl are each optionally substituted with from one to three substituents independently selected from R1';
- (b) R1', R26, R27, R28 and R31 are each independently selected from the group consisting of hydrogen, hydroxy, cyano, nitro, halo, oxo, C₁₋₆ alkyl, C₁₋₆ alkyl-COOR12, C₁₋₆ alkoxy, C₁₋₆ haloalkyl, C₁₋₆ haloalkyloxy, C₃₋₇ cycloalkyl, aryloxy, aryl-C₀₋₄-alkyl, heteroaryl, heterocycloalkyl, C(O)R13, COOR14, OC(O)R15, OS(O)₂R16, N(R17)₂, NR18C(O)R19, NR20SO₂R21, SR22, S(O)R23, S(O)₂R24, and S(O)₂N(R25)₂; R12, R13, R14, R15, R16, R17, R18, R19, R20, R21, R22, R23, R24 and R25 are each independently selected from the group consisting of hydrogen, C₁₋₆ alkyl and aryl;
- (c) R2 is selected from the group consisting of C₀₋₈ alkyl and C₁₋₄-heteroalkyl;
- (d) X is selected from the group consisting of a single bond, O, S, S(O)₂ and N;
- (e) U is an aliphatic linker wherein one carbon atom of the aliphatic linker is optionally replaced with O, NH or S, and wherein such aliphatic linker is substituted with from one to four substituents each independently selected from R30;
- (f) Y is selected from the group consisting of C and S;
- (g) E is C(R3)(R4)A or A and wherein

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- NR20SO₂R21, SR22, S(O)R23, S(O)₂R24, and
S(O)₂N(R25)₂; R12, R13, R14, R15, R16, R17, R18,
R19, R20, R21, R22, R23, R24 and R25 are each
independently selected from the group consisting
of hydrogen, C₁-C₆ alkyl and aryl;
- 5 (c) R2 is selected from the group consisting of C₀-C₈
alkyl and C₁₋₄-heteroalkyl;
- (d) X is selected from the group consisting of a
single bond, O, S, S(O)₂ and N;
- 10 (e) U is an aliphatic linker wherein one carbon atom
of the aliphatic linker is optionally replaced
with O, NH or S, and wherein such aliphatic linker
is optionally substituted with from one to four
substituents each independently selected from R30;
- 15 (f) Y is selected from the group consisting of S and
C;
- (g) E is C(R3)(R4)A; wherein
- (i) A is selected from the group consisting of
carboxyl, tetrazole, C₁-C₆ alkyl nitrile,
20 carboxamide, sulfonamide and acylsulfonamide;
wherein sulfonamide, acylsulfonamide and
tetrazole are each optionally substituted with
from one to two groups independently selected
from R⁷;
- 25 (ii) each R⁷ is independently selected from the
group consisting of hydrogen, C₁-C₆ haloalkyl,
aryl C₀-C₄ alkyl and C₁-C₆ alkyl;
- (iii) R3 is selected from the group consisting of
C₁-C₅ alkyl, and C₁-C₅ alkoxy; and
- 30 (iv) R4 is selected from the group consisting of
H, C₁-C₅ alkyl, C₁-C₅ alkoxy, aryloxy, C₃-C₆

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- independently selected from the group consisting of hydrogen, C₁-C₆ alkyl and aryl;
- (c) R₂ is selected from the group consisting of C₀-C₈ alkyl and C₁₋₄-heteroalkyl;
- 5 (d) X is selected from the group consisting of a single bond, O, S, S(O)₂ and N;
- (e) U is an aliphatic linker wherein one carbon atom of the aliphatic linker may be replaced with O, NH or S, and wherein such aliphatic linker is optionally substituted with R₃₀;
- 10 (f) Y is selected from the group consisting of C and S;
- (g) E is C(R₃)(R₄)A or A and wherein
- (i) A is selected from the group consisting of
- 15 carboxyl, tetrazole, C₁-C₆ alkyl nitrile, carboxamide, sulfonamide and acylsulfonamide; wherein sulfonamide, acylsulfonamide and tetrazole are each optionally substituted with
- from one to two groups independently selected
- 20 from R⁷;
- (ii) each R⁷ is independently selected from the group consisting of hydrogen, C₁-C₆ haloalkyl, aryl C₀-C₄ alkyl and C₁-C₆ alkyl;
- (iii) R₃ is selected from the group consisting of
- 25 hydrogen, C₁-C₅ alkyl, and C₁-C₅ alkoxy; and
- (iv) R₄ is selected from the group consisting of H, C₁-C₅ alkyl, C₁-C₅ alkoxy, aryloxy, C₃-C₆ cycloalkyl, and aryl C₀-C₄ alkyl, and R₃ and R₄ are optionally combined to form a C₃-C₄
- 30 cycloalkyl, and wherein alkyl, alkoxy, aryloxy, cycloalkyl and aryl-alkyl are each optionally

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